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Health and Environmental Effects Profile for Acetone Cyanohydrin

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR ACETONE CYANOHYDRIN

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16. ABSTRACT

The Health and Environmental Effects Profile for acetone cyanohydrin was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Acetone cyanohydrin has been determined to be a systemic toxicant. An Acceptable Daily Intake (ADI), defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect, for acetone cyanohydrin is 4.9 mg/day for oral exposure.

The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a relase as specified by CERCLA based on chronic toxicity. Existing data are insufficient to determine an RQ value.

17. KEY WORDS AND DOCUMENT ANALYSIS

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PREFACE

The first draft of this document was prepared by Syracuse Research Corporation under Contract No. 68-03-3112. This document was subsequently reviewed and revised by ECAO-Cincinnati and the Carcinogen Assessment Group, the Exposure Assessment Group and the Reproductive Effects Assessment Group of the Office of Health and Environmental Assessment.

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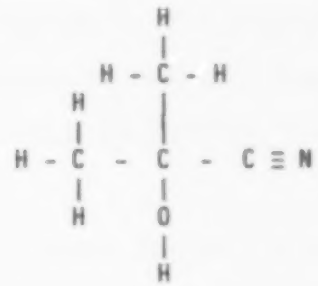
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BCF	Bioconcentration factor
bw	Body weight
CAS	Chemical Abstract Service
CS	Composite score
FEL	Frank-effect level
i.p.	Intraperitoneal
K_{oc}	Soil adsorption coefficient
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
LOAEL	Lowest-observed-adverse-effect level
MAC	Maximum acceptable concentration
MED	Minimum effective dose
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

Acetone cyanohydrin is also known as 2-hydroxy-2-methylpropanenitrile, α-hydroxyisobutyronitrile and 2-methyllactonitrile. The structure, empirical formula and molecular weight for acetone cyanohydrin are given below:



The empirical formula for acetone cyanohydrin is C_4H_7NO and the molecular weight is 85.10. The CAS Registry number for this compound is 75-86-5.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Acetone cyanohydrin is a colorless liquid at room temperature. Methods used for estimated parameters are discussed in the following text. Selected physical properties are listed below:

Melting point:	-20°C (Hawley, 1977)
Boiling point (23 mm Hg):	82°C (Hawley, 1977)
Density (19°C):	0.932 (Hawley, 1977)
Vapor pressure (20°C):	0.75 mm Hg (Weber et al., 1981)
Refractive index (20°C):	1.3996 (Hawley, 1977)
Water solubility (25°C):	1.0×10^6 ppm (U.S. EPA, 1985a)
Flash point (closed cup):	165°F (U.S. EPA, 1985a)

Conversion factor (20°C):	1 ppm = 3.54 mg/m³ (U.S. EPA, 1985a)
Henry's Law Constant:	8.4×10^{-8} atm-m³/mol (estimated)
BCF:	0.26 (estimated)
K_{oc}:	2 (estimated)

Acetone cyanohydrin is soluble in water, alcohol, ether, acetone and benzene. This compound decomposes at 120°C. The stability of acetone cyanohydrin in solution is pH dependent, with stability being greater in acidic pH. In basic pH, the compound decomposes. Thus, as pH 7.4, α-cyanohydrin may spontaneously release cyanide ions (NIOSH, 1978; U.S. EPA, 1985a).

1.3. PRODUCTION DATA

Acetone cyanohydrin is produced by reacting hydrogen cyanide and acetone catalyzed by a base at a temperature of ≤25°C (Smiley, 1981; Cholod, 1981). According to SRI (1984), the following manufacturers produce acetone cyanohydrin: CYRO Industries in Avondale, LA; E.I. Dupont Co. in Memphis, TN; Monsanto Co. in Texas City, TX; and Rohm and Haas Co., Deer Park, TX. According to the 1977 TSCA Production File, the following companies also manufacture acetone cyanohydrin: Kodak in Rochester, NY; E.I. Dupont Co. in Belle, WV; Deyussa Corporation in Theodore, AL; and one unidentified manufacturer (U.S. EPA, 1985b). In 1983, ~869 million pounds of acetone cyanohydrin were produced in the United States (USITC, 1984).

1.4. USE DATA

Acetone cyanohydrin is used as a raw material in the manufacture of insecticides and pharmaceutical intermediates and is also used as an intermediate in organic synthesis, principally to produce methyl methacrylate. It is used as a chelating agent and has been used in metal refining and separation (Cholod, 1981).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. AIR

Data regarding the fate and transport of acetone cyanohydrin were not located in the available literature as cited in the Appendix. NIOSH (1978) indicated there is no recommended method for analyzing acetone cyanohydrin in the atmosphere. It has been reported that at high temperatures acetone cyanohydrin vapor is oxidized in air (U.S. EPA, 1985a). Paucity of data on this compound makes it impossible to predict significant chemical removal process(es) of acetone cyanohydrin in air.

Transport methods of chemicals depend on their physical properties as well as their lifetime in the atmosphere. The complete miscibility of acetone cyanohydrin in water indicates that wet deposition to surface water and soil may be a significant transport process. Since the pH of rainwater is in general <pH 7.0, acetone cyanohydrin may not decompose significantly through this process yielding hydrogen cyanide.

2.2. WATER

Limited data regarding the fate and transport of acetone cyanohydrin were available. The aquatic fate of acetone cyanohydrin depends upon its chemical and photochemical reactivities and its rate of biological degradation. Lyman et al. (1982) stated that nitriles as a group are potentially susceptible to hydrolysis. Therefore, acetone cyanohydrin may hydrolyze in water. The stability of acetone cyanohydrin in solution has been reported to be pH dependent. Thus at pH >7.4, acetone cyanohydrin is expected to dissociate readily to acetone and hydrogen cyanide (NIOSH, 1978). Ishizaki et al. (1976) reported that acetone cyanohydrin was oxidized in aqueous solution at pH 7, 9 and 11. At pH 4, no effective oxidation took place. In acidic solution, acetone cyanohydrin may produce a carboxylic acid that is

susceptible to biodegradation, but this process may be inhibited by cyanide formation (U.S. EPA, 1985a) depending upon the resulting cyanide concentration. Slave et al. (1974) reported partial biodegradation of acetone cyanohydrin by activated sludge. No further details were available. Test results using both natural river water and sewage as seed suggest that various classes of nitriles appear to undergo different modes of bioconcentration. The behavior of acetone cyanohydrin is probably most analogous to that of lactonitrile because of the similarity in their chemical structures. Therefore, acetone cyanohydrin may undergo significant biodegradation (60-70% in 5 days at an initial concentration of up to 15 mg/ℓ for lactonitrile); however, lactonitrile dissociation leads to the formation of HCN and subsequent resistance to biodegradation at higher concentrations (Ludzack et al., 1958).

Using a vapor pressure of 0.75 mm Hg and a solubility of 1.0×10^6 ppm, Henry's law constant was calculated to be 8.4×10^{-8} atm-m³/mol. Based on this relatively low value, acetone cyanohydrin can be considered essentially nonvolatile (Lyman et al., 1982). Based on a BCF of 0.26 calculated from the equation given in Lyman et al. (1982), namely log BCF = 2.791 - 0.564 log S (S = water solubility in mg/ℓ), acetone cyanohydrin is not expected to bioaccumulate in fish.

2.3. SOIL

Insufficient data were available to predict possible chemical processes in soil. Acetone cyanohydrin could be highly mobile in soil, as indicated by a K_{oc} (partition coefficient standardized with respect to its organic carbon context) of 2 calculated from the following equation (Lyman et al.,

1982): log K_{oc} = -0.55 log S + 3.64. The low vapor pressure and miscibility of acetone cyanohydrin in water indicate that this chemical is not likely to volatilize from wet soil. In basic soils, however, HCN may be formed as a result of decomposition.

3. EXPOSURE

Pertinent data regarding environmental exposure to acetone cyanohydrin from water, food, and air were not located in the available literature as cited in the Appendix. The U.S. EPA STORET Data Base reported no listing for acetone cyanohydrin.

4. PHARMACOKINETICS

4.1. ABSORPTION

The cyanohydrins are absorbed rapidly through the gastrointestinal, respiratory and dermal routes (NIOSH, 1978). Acetone cyanohydrin is soluble in lipids, enhancing tissue absorption. Following acute exposures to acetone cyanohydrin, absorption is very rapid, with symptoms and death occurring within minutes or hours, depending on the exposure level. Industrial workers wear protective rubberized clothing because absorption of very small amounts is both rapid and toxic.

4.2. DISTRIBUTION

Cyanide distribution in the liver and brain after intraperitoneal injection of 9 mg/kg doses of acetone cyanohydrin to male CD-1 mice was reported by Willnite and Smith (1981). The mice were sacrificed 5 minutes after injection, and liver cyanide levels were 108.0±27.5 nmol/g (2.8±0.72 µg/g) and brain cyanide levels were 30.0±4.6 nmol/g (0.78±0.06 µg/g). Acetone cyanohydrin distribution displayed the same characteristics as its molar equivalent of free cyanide (Section 4.3.).

4.3. METABOLISM

Acetone cyanohydrin dissociates readily to yield hydrogen cyanide and an acetone (NIOSH, 1978); cyanide is converted to thiocyanate by the enzymatic action of rhodanase, which transfers sulfur from thiosulfate (U.S. EPA, 1985a).

The spontaneous dissociation of acetone cyanohydrin to free cyanide and acetone is supported by observations that acetone cyanohydrin and cyanide behave similarly *in vitro* and *in vivo*. Willhite and Smith (1981) studied the inhibition of the oxidation of cytochrome c *in vitro* by acetone cyanohydrin. In the presence of potassium cyanide or acetone cyanohydrin, the

reaction was inhibited in a concentration dependent manner, as previously observed in experiments with inorganic cyanides (Nicholls et al., 1972; Smith et al., 1977). Acetone cyanohydrin was rapidly and completely dissociated to its molar equivalent of free cyanide in *in vitro* systems.

Willhite and Smith (1981) demonstrated that the behavior of acetone cyanohydrin parallels that of the molar equivalent of cyanide *in vivo*. For example, the i.p. LD_{50}s in mice for acetone cyanohydrin (8.7 mg/kg or 2.65 mg CN^-/kg) and sodium cyanide (4.8 mg/kg or 2.54 mg CN^-/kg) were similar when compared as molar equivalent of cyanide. Time-to-death was 5.5 minutes for either compound. Pretreatment of mice with nitrite or thiosulfate, but not carbon tetrachloride, protected mice against i.p. administered lethal doses of acetone cyanohydrin or sodium cyanide. The levels of cyanide in mice following treatment with LD_{50} doses of aceteone cyanphydrin and sodium cyanide were 30 nmol/g (0.78 µg/g) and 24.9 nmol/g (0.65 µg/g) for the brain and 0.8 nmol/g (2.8 µg/g) and 87.8 nmol/g (2.3 µg/g) fo the liver, respectively.

4.4. EXCRETION

Pertinent data regarding the excretion of acetone cyanohydrin per se were not located in the available literature as cited in the Appendix. Thiocyanate derived from cyanide is excreted mainly in the urine (U.S. EPA, 1985c).

5. EFFECTS

5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of acetone cyanohydrin were not located in the available literature as cited in the Appendix, and this chemical is not scheduled for testing by NTP (1985).

5.2. MUTAGENICITY

Pertinent data regarding the mutagenicity of acetone cyanohydrin were not located in the available literature as cited in the Appendix.

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of acetone cyanohydrin were not located in the available literature as cited in the Appendix.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding the other reproductive effects of acetone cyanohydrin were not located in the available literature as cited in the Appendix.

5.5. CHRONIC TOXICITY

Shkodich (1966) studied the chronic toxicity of acetone cyanohydrin using 44 albino rats and 16 rabbits given doses of 0.00005, 0.0005, 0.005 and 1.33 mg/kg/day for 6 months. Details concerning the dosing schedule and route of administration were not provided. The animals were sacrificed after 6 months, and weight coefficient, vitamin C concentration of internal organs and the concentration of -SH in the cerebral cortex gray matter were determined. In rats, increases in erythrocytes, reticulocytes and hemoglobin and an increased vitamin C content in the liver and adrenals occurred at 1.33 mg/kg/day. Decreased -SH content in the brain and decreased serum catalase and cholinesterase were also observed at 1.33 mg/kg/day ($p<0.01$).

At 1.33 and 0.0005 mg/kg/day, there were functional changes in nervous system activity described as "attenuation of the processes of internal inhibition and certain intensification of the excitatory process." Changes in blood morphology, serum catalase and cholinesterase activity and vitamin C content were also seen at 0.0005 mg/kg/day. It was not clear if the changes observed at 1.33 and 0.0005 mg/kg/day also occurred at 0.005 mg/kg/day. No effects were observed in rats at 0.00005 mg/kg/day. In rabbits, there were no effects at $\leq$0.005 mg/kg/day. At 1.33 mg/kg/day, rabbits had a reduced rate of galactose utilization and decreased serum concentration of -SH groups, indicative of a disturbance or the glycogenic function of the liver.

White rats (50 per dose level) were administered 5 mg of acetone cyanohydrin orally 2 times/week for 3, 5 or 8 months (Motoc et al., 1971). A decrease of 15% in serum total protein, decreased albumin/globulin ratios and increased γ-globulin were observed. Levels of serum glycoproteins, were increased at 3 months, then decreased at 5 months and rose gradually by 8 months. β-Glucuronidase activity rose initially but was decreased at 8 months. Transaminase, aldolase and leucinaminopeptidase levels in serum were increased. Changes in hepatic protein metabolism and enzyme levels were also observed. Gross and histologic examination revealed increased gastric gland secretions and stomach ulcerations that increased in severity with an increase in duration of exposure. Reversible and irreversible dystrophic liver changes were present, with the reversible lesions being less prevalent with increasing exposure. The liver lesions were characterized by cell karyopyknosis, anisokaryosis, abnormal fat deposits, cytoplasmic thinning and lack of cytoplasmic granules. Kidney lesions were also observed but were not as severe as liver lesions.

Motoc et al. (1971) also exposed rats by inhalation to 10.2 g/m³ acetone cyanohydrin for 3, 5 or 8 months (groups of 50 rats/dose level). No further details of the exposure regimen were provided. Lung lesions included desquamation of bronchial epithelium and superficial ulcerations containing inflammatory cell infiltrations. After 8 months, irreversible kidney lesions affecting the entire nephron were observed. Irreversible, severe hepatic lesions similar to those associated with oral ingestion were also observed.

5.6. OTHER RELEVANT INFORMATION

Human ingestion of acetone cyanohydrin has been reported by Sunderman and Kincaid (1953). A plant worker drank an unknown quantity of alcohol from a storage tank, which also contained traces of acetone cyanohydrin. The person lost consciousness; subsequently, he regained consciousness, but died 12 hours after ingestion of the mixture.

Several fatalities have been reported from dermal exposure to acetone cyanohydrin. A plant worker whose clothing was splashed with an unknown quantity of acetone cyanohydrin became nauseated 3 hours later, and became unconscious and convulsive; the worker died 6.5 hours after the exposure (Sunderman and Kincaid, 1953). Krefft (1955) reported a chemical factory accident in which a 51-year-old female worker was splashed on the face and clothing with 19 ℓ acetone cyanohydrin when a glass flask burst. The exposed skin area was washed, but the contaminated clothing was not removed. Ten minutes after exposure, tonic-clonic convulsions occurred and the woman died 80 minutes after exposure. At autopsy, hyperemia of the brain and skin, dilatation of the right side of the heart, hyperemia and moderate edema of the lungs, and moderate gastric irritation were noted. Sunderman and Kincaid (1953) also reported a nonfatal case in which three individuals

were dermally exposed while packing pumps for storage tanks. The workers lost consciousness but were revived with fresh air and washing of the exposed areas. Symptoms included cardiac palpitation, headache, nausea and vomiting, but no permanent injury occurred.

Lang and Stintzy (1960) reported a case of occupational exposure in a 19-year-old worker at a chemical synthesis plant. Approximately 30-40 mL acetone cyanohydrin wet a portion of his clothing while he was dismantling a conduit. Skin contact with the wet clothing was for 40-60 minutes and exposure to the dry residue was for ~5.5 hours. Five hours after the initial exposure, the individual experienced headache, retching, painful throat constriction, weakness, numbness, dizziness and vomiting. The person was taken to a hospital in a deep coma 8.5 hours after exposure. His body was cyanotic, reflexes were absent and tonic-clonic convulsions were occurring. The victim regained consciousness the next morning; he remained hospitalized for 10 days and returned to work 1 month after the exposure.

Thiess and Hey (1969) reported the exposure of a 23-year-old man to acetone cyanohydrin while filling drums from a rubber hose connected to a tank car (the worker was not wearing protective rubber gloves or clothing). One of the cotton gloves that he used became soaked and the individual placed it in a trouser pocket. Vomiting occurred 5 minutes later; the man lost consciousness within 10 minutes. Tonic-clonic convulsions also occurred. Removal of the glove and treatment with sodium nitrite and sodium thiosulfate alleviated the symptoms. The man was hospitalized for 3 days, and returned to work 8 days later. Zeller et al. (1969) also described three other cases of human exposure to acetone cyanohydrin, but no details concerning effects are available (NIOSH, 1978).

Sunderman and Kincaid (1953) exposed rats by inhalation to acetone cyanohydrin at air saturation levels. Range-finding values for acute toxicity were determined; in 10 minutes, 50% of the rats died and after 11 minutes, 15 rats died, with all rats collapsing within an average time of 4 minutes. These authors also studied acute toxicity by skin absorption in guinea pigs, using a mixture of 94.7% acetone cyanohydrin containing 0.25% hydrogen cyanide. The percutaneous (dermal) LD_{50} was 140 mg/kg. In experiments with rats, Sunderman and Kincaid (1953) determined that a combination of sodium nitrite and sodium thiosulfate administered before exposure to acetone cyanohydrin prevented the death of animals exposed to the vapor.

Krefft (1955) dermally exposed three male guinea pigs to acetone cyanohydrin by painting one animal on both ears, painting another animal on a small area of its shaved back or by applying a 2x5 cm gauze sponge soaked with the chemical to the shaved back of a third animal. Within 7 minutes all animals exhibited difficulty in breathing and excreted urine and feces. Within 31-40 minutes, respiratory paralysis was evident and all animals died within 48-51 minutes. An autopsy revealed local hyperemia and swelling of exposed areas; lung edema; hyperemia and edema of liver and brain; dilatation of the right side of the heart; extensive subpleural and subepicardial echymoses; and acute venous obstruction in major organs and exposed areas of the skin.

Smyth et al. (1962) reported mortality data for rats exposed to vapors of acetone cyanohydrin for 4 hours. All six rats exposed to 125 ppm (435 mg/m^3) for 4 hours died within 14 days following exposure. In six rats exposed to 62.5 ppm (217 mg/m^3) for 4 hours, 2/6 rats died after 14 days. Exposure to concentrated vapor inhalation for up to 5 minutes resulted in no deaths.

A summary of LD_{50} values for mice, rats, guinea pigs and rabbits is presented in Table 5-1.

Loomis (1978) and Doull et al. (1980) discussed the acute toxicity caused by the release of cyanide ion from compounds like acetone cyanohydrin and other nitriles. The toxicity is primarily due to formation of an irreversible complex between the cyanide ion and the iron moiety in the tissue enzyme ferric cytochrome oxidase (or cytochrome a_3) found in the electron transport system of mitochondria. Cyanide ions also react with a number of other metal containing enzymes. Aerobic metabolism is dependent on ferric cytochrome oxidase, and its inhibition causes tissue hypoxia and cellular destruction because metabolic processes can no longer continue without oxygen utilization.

Sunderman and Kincaid (1953) used nitrite as a reducing agent to convert oxyhemoglobin to methemoglobin. The cyanide ion has a greater affinity for methemoglobin than for cytochrome a_3. In the presence of cyanide, methemoglobin is converted to a stable, nontoxic hemoglobin pigment, cyanmethemoglobin. The conversion of the oxyhemoglobin to methemoglobin in red cells provides additional sources of ferric ion for the reaction with cyanide ion, sparing the tissue enzymes from inactivation. The methemoglobin cannot carry oxygen in the red cell, but replacement of useless red cells is fairly rapid by the body compared with cytochrome a_3 inactivation in tissues. Moreover, if sufficient cyanide complexes with this enzyme in tissues such as the brain are formed, central respiratory arrest will result leading to death. Methemoglobin is dissociated slowly, releasing small amounts of cyanide ion which then can be converted to thiocyanate by hepatic metabolism. In the liver and kidney, the enzyme (rhodanase) is found in high concentrations and is able to convert cyanide to thiocyanate. Sodium

TABLE 5-1

LD_{50} Values for Acetone Cyanohydrin

Route	Species	Concentration (mg/kg)	Reference
Oral	mouse	14	NIOSH, 1985
Oral	rat	16	Smyth et al., 1962
Oral	guinea pig	9	Shkodich, 1966; NIOSH, 1985
Oral	rabbit	13.5	Shkodich, 1966; NIOSH, 1985
Dermal	rabbit	16	Smyth et al., 1962
Dermal	guinea pig	140	Sunderman and Kincaid, 1953
Dermal	guinea pig	150	NIOSH, 1985
Intraperitoneal	mouse	8.39	Yoshikawa, 1968
Intraperitoneal	mouse	8.7	Willhite and Smith, 1981

thiosulfate administration aids this process by providing an additional source of sulfur. Methemoglobin is also restored to a functional blood pigment by intracellular reductase systems. Therefore, concurrent administration of thiosulfate and nitrite provides a basus for antidotal therapy.

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

Few data regarding the responses of freshwater and marine organisms to acetone cyanohydrin exposure were available for a comprehensive evaluation of aquatic toxicity. Dawson et al. (1977) conducted an investigation of the acute static toxicity of acetone cyanohydrin to a freshwater and a marine species. The 96-hour LC_{50} values of 0.57 mg/ℓ at 23°C and 0.50 mg/ℓ at 20°C were determined for bluegill, Lepomis macrochirus, and tidewater silversides, Menidia beryllima, respectively. The LC_{50} values of 1.7 and 0.9 mg/ℓ for the golden orfe, Leuciscus idus melanotus, were determined at two independent laboratories (Juhnke and Luedemann, 1978); however, the length of exposure period and test methods were not described. The 96-hour TLM for acetone cyanohydrin is 1-10 ppm (1-10 mg/ℓ) (Sax, 1984).

6.2. CHRONIC EFFECTS

Data regarding the chronic toxicity of acetone cyanohydrin to aquatic organisms were not located in the available literature as cited in the Appendix.

6.3. PLANT EFFECTS

Data regarding the effects of acetone cyanohydrin to aquatic plants were not located in the available literature as cited in the Appendix.

6.4. RESIDUES

Data regarding acetone cyanohydrin residues in aquatic organisms were not located in the available literature as cited in the Appendix.

6.5. OTHER RELEVANT INFORMATION

Additional data regarding the toxic effects of acetone cyanohydrin to aquatic organisms were not located in the available literature as cited in the Appendix.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The recommended ceiling limit for occupational exposure to acetone cyanohydring is 1 ppm or 3.5 mg/m³ for any 15-minute period (NIOSH, 1978). This standard is based on the observations that acetone cyanohydrin is 18.3 times more toxic than acetonitrile by inhalation and because α-cyanohydrins dissociate readily to release hydrogen cyanide.

MAC levels of 0.9 mg/m³ (0.3 ppm) were established in Hungary and the USSR (NIOSH, 1978). Italy set an 8-hour TWA limit of 70 mg/m³ (20 ppm) and Rumania established a TWA limit of 15 mg/m³ (4 ppm) and a MAC level of 25 mg/m³ (7 ppm). Both the USSR and Rumania warn of possible skin absorption.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms were not located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Pertinent data regarding carcinogenicity, mutagenicity or teratogenicity of acetone cyanohydrin were not located in the available literature as cited in the Appendix. The compound would be appropriately placed in Group D, not classified, using the CAG evidence assessment groupings (U.S. EPA, 1984).

Two subchronic oral studies are available for consideration in the risk assessment; however, the data are poor and limited in range of dosage.

In the Russian study by Shkodich (1966) rats exhibited nervous system changes, serum and liver enzyme changes and aberrations in hematological values at doses $\geq$0.0005 mg/kg/day. Few effects were observed in rabbits given 1.33 mg/kg/day and no effects were observed at $\leq$0.005 mg/kg/day. However, details concerning dosing schedule and route of administration of acetone cyanohydrin were not provided, therefore, this study is inappropriate for calculation of an ADI.

Motoc et al. (1971) orally administered 5 mg acetone cyanohydrin to rats 2 times/week for 3, 5 or 8 months. After initial exposure to acetone cyanohydrin, increased levels of transaminase, aldolase and leucinaminopeptidase were observed. With increased duration of exposure, glutamic pyruvic transaminase and glutamic oxaloacetic transaminase levels increased in the liver. Serum glycoproteins increased after 3 months of exposure; subsequently, there was a decrease and then a gradual increase to below normal values after 8 months of exposure. β-glucuronidase activity increased with initial exposure, but fell below normal levels after prolonged ingestion of acetone cyanohydrin. A 15% decrease in total serum proteins and decreased albumin/globulin ratios with increased amounts of γ-globulin were also observed. Increased gastric gland secretions and ulcerations, becoming more

severe with prolonged exposure and liver lesions, both reversible and irreversible, were also observed. Hepatic cell abnormalities included paryopyknosis, anisokaryosis, abnormal fat deposits, cytoplasmic thinning and lack of cytoplasmic granules. Less severe kidney lesions were also noted. Similar results were observed in rats exposed to acetone cyanohydrin by inhalation at 10.2 g/m^3 (schedule unspecified) for up to 8 months. Inherent problems with this study were the use of only one dose level and the lack of control animals. Furthermore, the intermittent bolus exposures of 5 mg/rat, 2 days/week in the oral study does not adequately represent the steady-state exposure obtained under truly chronic exposure conditions, (i.e., long-term administration in diet or drinking water). Therefore, the study of Motoc et al. (1971) is inappropriate for use in the derivation of an ADI for acetone cyanohydrin.

Considering the problems discussed above, it may be more appropriate to base an ADI for acetone cyanohydrin by analogy to cyanide, for which a better data base exists (U.S. EPA, 1985c). Supportive evidence is available concerning dissociation of acetone cyanohydrin into acetone and hydrogen cyanide components under physiological conditions (Gould, 1959; NIOSH, 1978). Further supportive evidence was presented from the studies of Willhite and Smith (1981). These authors demonstrated that acetone cyanohydrin readily dissociates to produce cyanide in vitro, that acetone cyanohydrin was not metabolically converted to cyanide by microsomal liver enzymes, and that acetone cyanohydrin is similar to hydrogen cyanide in its toxic effects.

Willhite and Smith (1981) intraperitoneally administered acetone cyanohydrin and sodium cyanide at approximately equimolar doses of cyanide to mice. Using the LD_{50} for both compounds (8.7 mg/kg for acetone cyanohydrin 30.5% cyanide which equals 2.65 mg CN^-/kg; and 4.8 mg/kg sodium

cyanide, 53% cyanide which equals 2.54 mg CN^-/kg), these authors found liver and brain cyanide levels for both compounds to be similar. Acetone cyanohydrin doses of 8.7 (2.65 mg cyanide) mg/kg produced liver cyanide levels of 108 nmol/g (2.8 μg/g) and brain cyanide levels of 30 nmol/g (0.78 μg/g). Sodium cyanide doses of 4.8 (2.54 mg cyanide) mg/kg produced liver cyanide levels of 87.8 nmol/g (2.3 μg/g) and brain cyanide levels of 24.9 nmol/g (0.65 μg/g).

Protection from cyanide deposition in tissues by pretreatment with sodium thiosulfate (Doull et al., 1980; U.S. EPA, 1985c) had similar positive effects for both compounds (Willhite and Smith, 1981). Carbon tetrachloride pretreatment, to inhibit the activity of liver enzymes, was ineffective in reducing cyanide levels in brain and liver for both acetone cyanohydrin and sodium cyanide. Finally, both compounds inhibited oxidation of cytochrome c by molecular oxygen in vitro, as mediated by cytochrome c oxidase.

Under all conditions tested by Willhite and Smith (1981), acetone cyanohydrin exhibited effects similar to its molar equivalent in free cyanide.

For cyanide, a study by Howard and Hanzal (1955) was used as the basis for calculation of an ADI (U.S. EPA, 1985c). A NOAEL of 10.8 mg CN^-/kg bw/day was determined. In this 2-year study, Carworth Farms rats (10/sex/group) were fed diets containing hydrogen cyanide at concentrations of 0, 100 or 300 mg hydrogen cyanide/kg diet. Based on food consumption and weight gain data, estimated daily dosage levels were 4.6 and 10.8 mg CN^-/kg/day for females and 3.6 and 7.5 mg CN^-/kg/day for males. No treatment-related effects of any kind were observed. Dividing 10.8 mg CN^-/kg/day by an uncertainty factor of 500 (10 for interspecies extrapolation, 10 to protect the most susceptible individuals, and 5 because the

cyanide source was dietary) results in an ADI of 0.0216 mg CN^-/kg/day or 1.5 mg CN^-/day for a 70 kg man. On an equimolar basis, the ADI for cyanide is equivalent to an ADI for acetone cyanohydrin of 0.0707 mg/kg/day or 4.9 mg/day for a 70 kg man.

It should be noted that the above ADI for acetone cyanohydrin based on analogy to cyanide is tenable only if the rate constants for absorption, distribution, binding to cytochrome oxidase, detoxification and excretion of cyanide following exposure to cyanide and acetone cyanohydrin are identical, and if the breakdown of acetone cyanohydrin to cyanide is instantaneous. Because data regarding these rate constants are insufficient, the ADI of 4.9 mg/day for acetone cyanohydrin should be regarded as provisional.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

The available data on the toxicity of acetone cyanohydrin following long-term exposure were discussed in Section 5.5. and are summarized in Table 9-1. None of the data are suitable for the derivation of the RQ. In the Russian study (Shkodich, 1966) in rats and rabbits, the route of administration and dosing schedule were not reported. In the French study (Motoc et al., 1971), the rats treated orally were dosed only 2 days/week with a bolus, which does not represent the steady-state exposure obtained under chronic conditions. Furthermore, since only one dose level was used, a threshold for the effects observed at that dose level cannot be defined; hence, an MED cannot be calculated. For the inhalation experiment (Motoc et al., 1971), the exposure schedule was not provided, precluding the calculation of a dose. As with the oral experiment, only one exposure level was used. In neither the oral nor the inhalation experiment were control rats used.

Therefore, as indicated in Table 9-2, data are not sufficient to calculate an RQ.

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

Pertinent data regarding carcinogenicity of acetone cyanohydrin were not located in the available literature as cited in the Appendix. Therefore, acetone cyanohydrin is placed in IARC Group 3, that is, it cannot be classified as to its carcinogenic potential for humans. This is equivalent to Group D, not classified, using the CAG ranking system (U.S. EPA, 1984).

TABLE 9-1

Toxicity Summary for Acetone Cyanohydrin[a]

Route	Species/ Strain	Number at Start	Vehicle/Physical State	Dosage/Exposure	Dose	Response	Reference
NR	rat/albino	44	NR	0.00005, 0.0005, 0.005 and 1.33 mg/kg/day for 6 months (dosing schedule NR)	0.00005, 0.0005, 0.005 and 1.33[b]	No effects at 0.00005 mg/kg; functional changes in nervous system activity at 0.0005 and 1.33 mg/kg/day; increased vitamin C content of liver, decreased -SH content in brain, decreased serum catalase and cholinesterase. No effects were reported at 0.005 mg/kg/day.	Shkodich, 1966
NR	rabbit/NR	16	NR	0.00005, 0.0005, 0.005 and 1.33 mg/kg/day for 6 months (dosing schedule NR)	0.00005, 0.0005, 0.005 and 1.33[b]	No effects at ≤0.005 mg/kg; at 1.33 mg/kg/day, reduced rate of galacto[illegible] utilization, decreased concentration of serum -SH.	Shkodich, 1966
Oral	rat/NR	50/group	NR	5 mg/rat, 2 days/ week for 3, 5 or 8 months	4.09 mg/kg/day[c]	Decreased serum protein, changes in serum enzyme levels, stomach ulcers, liver and kidney lesions	Motoc et al., 1971
Inhalation	rat/NR	50/group	air	10.2 g/m³	unknown[d] (exposure schedule NR) 3, 5 or 8 months	Histopathologic lesions in lung, liver and kidney	Motoc et al., 1971

[a]Sex of animals and purity of compound not reported

[b]The dosing schedule was assumed to be 7 days/week.

[c]The dose was calculated by expanding the exposure over 7 days/week and dividing by the assumed body weight of a rat (0.35 kg).

[d]The number of hours/day and days/week of exposure were not provided, precluding any calculation of a dose.

NR = Not reported

0694p

10/15/85

TABLE 9-2

Acetone Cyanohydrin

Minimum Effective Dose (MED) and Reportable Quantity (RQ)

Route:	
Dose:	
Effect:	
Reference:	
RV_d:	
RV_e:	
Composite Score:	
RQ:	Data are not sufficient for deriving an RQ

Acetone cyanohydrin

10. REFERENCES

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320
TOXLINE
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP

These searches were conducted in July, 1984. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

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